

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Physical Activity as Intervention for Age-Related Loss of Muscle Mass and Function: Protocol for a Randomized Controlled Trial (the LISA study)
<b>AUTHORS</b>	Eriksen, Christian; Garde, Ellen; Reisle, Nina; Wimmelmann, Cathrine; Bieler, Theresa; Ziegler, Andreas; Gylling, Anne; Dideriksen, Kasper; Siebner, Hartwig; Mortensen, Erik; Kjaer, Michael

### VERSION 1 - REVIEW

<b>REVIEWER</b>	F.J. Tarazona-Santabalbina Hospital Universitario de la Ribera. Alzira, Valencia, Spain
<b>REVIEW RETURNED</b>	09-Sep-2016

<b>GENERAL COMMENTS</b>	<p>The authors have presented a clear and well-run manuscript to the study objectives. However, some aspects should be clarified</p> <p>Abstract. Page 4. Lines 20. "the impact of muscle strength...on cognitive function...remain speculative". Speculative means : pertaining to, of the nature of, or characterized by speculation, contemplation, conjecture, or abstract reasoning; theoretical, rather than practical. There is not enough scientific support to consider the relationship between muscle and cognitive function as speculative</p> <p>AIMS. Page 9. Line 29. The authors do not use batteries changes as the Short Physical Performance Battery or Edmonton Frailty Scale , which can detect small changes in different domains. Nor do they include analytical determinations between plasma levels of total protein, albumin or BDNF , related to cognitive improvement after performing physical activity. It would be advisable that the authors include some of these variables or justify their absence.</p> <p>Participants. Page 11. Between 62 and 70 years of age, 6-10% of subjects had frailty criteria . However , no measurement of frailty is not mentioned, nor frailty is included in the inclusion or exclusion criteria , neither a possible subanalysis mentioned depending on the robust pre-frail or frail state. Also not an analysis of the functional status in activities of daily living ( Barthel and Lawton scales ) , some of which may be limited by prevalent chronic diseases in this age range is performed . It would be advisable that the authors provide additional information.</p> <p>Interventions: Page 14. Line 21. The control group performed a cultural or social activity, which modifies its usual routine and can</p>
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	<p>help improve cognitivos and physical parameters . It would be advisable that the authors justify the choice of this activity instead of allowing the control group maintained their normal routine.</p> <p>Page 22. The authors have decided to use as its main objective the extensor leg power . There are other possibilities with the same or greater reproducibility as the speed of the march , which also allows you to associate the results to different health outcomes. Also among the targets would be advisable to include the scale of Tinetti and , since the monitoring period is extended to 10 years and lestudio could be enriched studying the cumulative incidence of falls in each group , the number of hospitalizations , and clinical parameters such as incidence of cognitive impairment , diabetes , hypertension, vascular events , etc.</p> <p>Finally , I would like to congratulate the authors for the quality of design presented . I am convinced that the good results can be obtained in this study</p>
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<b>REVIEWER</b>	Ivan Bautmans Frailty in Ageing research department Vrije Universiteit Brussel Laarbeeklaan 103 B-1090 Brussels, Belgium
<b>REVIEW RETURNED</b>	11-Sep-2016

<b>GENERAL COMMENTS</b>	<p>This paper describes the study protocol of an ongoing RCT focusing on the effects of 2 resistance training programs on knee extensor muscle power compared to control in older individuals. The authors defined also a large set of secondary outcomes, among which cognitive functioning and MRI scans of the brain. The exercise intervention will last 1 year and participants are followed-up for 10 years.</p> <p>The study protocol is very well written and comprehensive. The study is well designed and very ambitious in nature. To date, most published resistance exercise interventions are aiming to evaluate effects on short to moderate term. The long-term follow-up proposed here is a strong aspect.</p> <p>Given the potentially important results that will be generated by this study, I recommend to accept this protocol for publication.</p> <p>Although the study is ongoing, I have some minor recommendations:</p> <p>1/ The accommodation period is relatively long (6-8 weeks). In my experience, older persons (even at very high age, untrained and presenting chronic conditions) tolerate very well intensive resistance training. The motivation for this long accommodation period can be better explained in the protocol. This is potentially important for the readers in order to avoid that resistance training would be considered as potentially dangerous for older persons.</p> <p>2/ Time points of measurements: based on table 2, it seems that no single outcome will be measured before the end of the 1 year</p>
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	<p>intervention. I would advise also an intermediate evaluation for some outcomes. Especially regarding the exercise adherence a systematic assessment at a regularly basis might be useful in order to be able to evaluate dose-response relationships as well as to identify subgroups of participants who trained less during the 1 year intervention. Besides adherence, as defined in the protocol as weekly training frequency (on a 5-point scale); also compliance to the exercise intensity (number of repetitions, resistance applied, number of series, number of exercises etc.) could be recorded in a more quantitative manner.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: F.J. Tarazona-Santabalbina

Q1

Abstract. Page 4. Lines 20. "the impact of muscle strength...on cognitive function...remain speculative". Speculative means : pertaining to, of the nature of, or characterized by speculation, contemplation, conjecture, or abstract reasoning;theoretical, rather than practical. There is not enough scientific support to consider the relationship between muscle and cognitive function as speculative

A1

We recognize that the word "speculative" is not suitable in this context. We have rephrased to "uncertain", which we believe is an appropriate word for describing the lack of evidence in the relation between resistance training and cognition/brain structure in older adults.

Q2

AIMS. Page 9. Line 29.

The authors do not use batteries changes as the Short Physical Performance Battery or Edmonton Frailty Scale , which can detect small changes in different domains. Nor do they include analytical determinations between plasma levels of total protein, albumin or BDNF, related to cognitive improvement after performing physical activity. It would be advisable that the authors include some of these variables or justify their absence.

A2

We appreciate the Short Physical Performance Battery (SPPB) and the Edmonton Frailty Scale (EFS) as valid and reliable measures of small changes in physical performance and frailty in older adults and frail individuals. In the LISA study however, we are more interested in larger changes and variations in skeletal muscle function, and since the participants are expected to be less "frail" than the background population, they might perform too good to detect small changes on the SPPB (ceiling effect).

Determination of plasma levels of total protein, albumin and BDNF is not included in the routine blood analysis and not approved by the ethical committee. However, we have established a biobank, where we keep blood samples from all participants, and we agree that a relation of these blood measures to cognitive changes would be interesting to pursue in a sub-study after additional ethical approval.

Q3

Participants. Page 11.

Between 62 and 70 years of age, 6-10% of subjects had frailty criteria . However , no measurement of frailty is not mentioned, nor frailty is included in the inclusion or exclusion criteria , neither a possible subanalysis mentioned depending on the robust pre-frail or frail state. Also not an analysis of the

functional status in activities of daily living ( Barthel and Lawton scales ), some of which may be limited by prevalent chronic diseases in this age range is performed . It would be advisable that the authors provide additional information.

A3

In the LISA study protocol, frailty is not mentioned in the in- and exclusion criteria, and we have currently no plans for assessing frailty in a sub-analysis. We recognize frailty as an important measure of vulnerability in a population of older adults. However, though we aim to represent the background population, it is obvious to us that the LISA participants are healthier. To be eligible, the participants have to be able not only to perform an extensive training program but also to commute between home and the hospital / training facilities, and this precludes the more frail individuals from participation.

In long-term follow-up assessments (4, 7, 10 years), it may be interesting to evaluate group differences in frailty (i.e. the EFS) and/or activities of daily living (i.e. Lawton and Barthel Scales). The study design allows sub-studies, which makes it possible to pursue these questions at a later time-point. Off course this will require additional ethical approval.

We have mentioned in the “Participants” section that ability to commute to the hospital and training facilities is a criterion for participation, and we have elaborated on the matter of frailty in the discussion section.

Q4

Interventions: Page 14. Line 21. The control group performed a cultural or social activity, which modifies its usual routine and can help improve cognitivos and physical parameters . It would be advisable that the authors justify the choice of this activity instead of allowing the control group maintained their normal routine.

A4

The training groups attend training in groups on a weekly basis, which in addition to the physical training introduces a regular social contact to the participants. Instead of allowing the control group participants to maintain their normal routine, we chose to introduce social activities without a physical content to isolate the possible benefits of physical training from those of the social contact. We recognize that cultural as well as social activities per se may have a positive effect on both cognitive and physical outcomes, and that this makes it harder to demonstrate a potential benefit of training. In the power calculations we have actually anticipated a small increase in the primary outcome in the control group. If we do find, that resistance training is not superior to a social/cultural intervention with respect to physical and cognitive performance, this is also an interesting finding. We have added this discussion to the "discussion" section.

Q5

Page 22.

The authors have decided to use as its main objective the extensor leg power . There are other possibilities with the same or greater reproducibility as the speed of the march , which also allows you to associate the results to different health outcomes. Also among the targets would be advisable to include the scale of Tinetti and , since the monitoring period is extended to 10 years and lestudio could be enriched studying the cumulative incidence of falls in each group , the number of hospitalizations , and clinical parameters such as incidence of cognitive impairment , diabetes , hypertension, vascular events , etc.

A5

We appreciate that gait speed is a valid and reproducible measure of physical function in older adults, which can be associated to different health outcomes. However, in this non-clinical setting we have chosen “leg extensor power” as primary outcome, which focuses more isolated on skeletal muscle

function, correlates well with physical function in older adults, and also captures performance of the more fit individuals in the population. We have elaborated on this in the “discussion” section in the protocol.

Clinical health related outcomes, like the incidence of falls, number hospitalization, incidence of cognitive impairment, diabetes, hypertension, vascular events etc. are indeed relevant to investigate. Self-reported health status and disease incidence is assessed with the “background and lifestyle” questionnaire. In addition, it is possible in Danish registries, after ethical approval, to investigate incidence of all diseases resulting in contact to the health care system in our cohort.

Reviewer: 2

Reviewer Name: Ivan Bautmans

Q1

1/ The accommodation period is relatively long (6-8 weeks). In my experience, older persons (even at very high age, untrained and presenting chronic conditions) tolerate very well intensive resistance training. The motivation for this long accommodation period can be better explained in the protocol. This is potentially important for the readers in order to avoid that resistance training would be considered as potentially dangerous for older persons.

A2

We agree that resistance training in older adults is relatively safe, and two or three weeks accommodation is usually sufficient. Because the participants are untrained, and because the intervention period is long and we also hope that the participants continue with resistance training after the intervention, we have chosen to put an extra effort into teaching proper techniques. In the accommodation period participants go from no training to training three times a week. Then we increase the volume further going from one to three sets of each exercise. Finally, we also increase the load in the accommodation period, when the exercise quality is acceptable and when the participants are comfortable with the exercises, but we focus more on exercise quality than on intensity.

We recognize that the reason for choosing a relatively long accommodation period is incompletely explained in the protocol and have elaborated on the subject in the “methods” section under “interventions”.

Q2

2/ Time points of measurements: based on table 2, it seems that no single outcome will be measured before the end of the 1 year intervention. I would advise also an intermediate evaluation for some outcomes. Especially regarding the exercise adherence a systematic assessment at a regularly basis might be useful in order to be able to evaluate dose-response relationships as well as to identify subgroups of participants who trained less during the 1 year intervention. Besides adherence, as defined in the protocol as weekly training frequency (on a 5-point scale); also compliance to the exercise intensity (number of repetitions, resistance applied, number of series, number of exercises etc.) could be recorded in a more quantitative manner.

A2

There are no plans for evaluating the outcomes between baseline and the end of the 1 year intervention. Though this would be interesting with regards to dose-response relationships of training, it is not possible to include in the current protocol. As explained in the protocol under “interventions”, we keep training diaries, where participants record all training days as well as the exercises performed, number of repetition, sets, and the training load. Also, participants are encouraged to register any reasons for not performing the intended training program. The physical trainers monitor the training registration after each training session in the HRT group and on a weekly basis in the MIT

group. We believe that the training diaries is an acceptable continuous quantitative measure of training compliance over the one year intervention period, and though we cannot conclude anything about the effect of training duration on physical outcomes, we can estimate a dose-response relationship between average training volume and physical outcomes after one year. Moreover, it will be possible to analyze load progression through the intervention and relate this to training frequency. We use the adherence questionnaire (5-point scale) to assess training adherence after the intervention, but we recognize that this is not an optimal quantitative assessment.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	F.J. Tarazona-Santabalbina Hospital Universitario de la Ribera.
<b>REVIEW RETURNED</b>	09-Oct-2016

<b>GENERAL COMMENTS</b>	The authors have addressed adequately the responses. The clinical design is now clearer to the reader of the manuscript. It better understands the strategy of the authors to define with more precision the main results they want to measure. From my point of view, the manuscript meets the requirements to be published.
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